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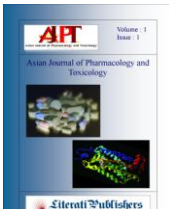

REVIEW ARTICLE

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Insulin Drug Delivery: Novel Approaches

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ABSTRACT
The drug delivery systems (DDS) are interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. Till recent, injections remained the most common means for administering therapeutic proteins and peptides such as insulin, because of their poor oral bioavailability. Designing and formulating a polypeptide drug delivery has been a persistent challenge because of their unfavorable physicochemical properties, which includes enzymatic degradation, poor membrane permeability and large molecular size. Due to the inconvenience of insulin injections, various approaches have been attempted to formulate insulin for administration by non-injectable routes. Various strategies currently under investigation include chemical modification, formulation vehicles and use of enzyme inhibitors, absorption enhancers and mucoadhesive polymers. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, lipoproteins, liposomes, gelfoams, niosomes and micelles. Different approaches to deliver insulin including transdermal, transmucosal, pulmonary route using dry aerosols and inhalers, smart hydrogels, nasal delivery and oral delivery has resulted in recent developments in treatment of diabetes. This review summarizes different pharmaceutical approaches which overcome various physiological barriers that help to improve bioavailability that ultimately achieve formulation goals for insulin delivery by a patient-friendly route.

Key words – noninvasive route, insulin, drug carriers

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1. INTRODUCTION

Diabetes mellitus is one of the most prevalent endocrinopathy characterized by the body's inability to produce or respond properly to insulin, a hormone used to convert blood glucose into energy, which leads to an elevation in the blood glucose (hyperglycemia). In normal individuals, a rise in blood glucose levels (such as that which occurs immediately following eating) triggers the islet beta cells of the pancreas to secrete insulin, a peptide hormone, into the bloodstream. The insulin binds to insulin receptors located on a number of cell types, notably muscle cells, and thereby signals the cells to increase the rate of glucose uptake into the cells[1]. As the blood glucose returns to normal pre-prandial levels, the amount of insulin in the blood also drops. In the absence of insulin, blood glucose levels would rise to dangerously high levels (a condition termed hyperglycemia), possibly resulting in death. Too much insulin causes abnormally low blood glucose levels (hypoglycemia), which is also dangerous and possibly fatal. In a normal individual, built-in feedback loops regulating the secretion of insulin and its clearance from the systemic circulation prevent both hyperglycemic and hypoglycemic conditions from occurring.

Diabetes mellitusis affecting a large percentage of population all over the world. Each year, diabetes contributes to considerable deaths through its complications such as heart disease, kidney failure and stroke. Approximately 40% of the 135 million people diagnosed with diabetes worldwide are receiving insulin as a component of their therapy [2].Despite its worldwide use, conventional subcutaneous insulin injection is relatively painful and inconvenient, with poor patient acceptability.

Alternative methods of insulin delivery have been the focus of research for the past few decades. The increased biochemical and structural complexity of proteins compared with conventional drug-based pharmaceuticals make formulation design for delivery of therapeutic proteins (including insulin) a very challenging task. The key to the success of protein as pharmaceuticals is to have in place an efficient drug delivery system that allows the protein drug to gain access to their target sites at the right time and for the proper duration. Four factors that must be considered to fulfill this goal are route of administration, pattern of drug release, method of delivery, and fabrication of formulation. Insulin administration has been a prominent topic for researchers in last few decades. A large number of significant work has been published in this regard. A formulation for oral administration of insulin was designed by Kidron et al.[3]. A proposed pharmaceutical compositions for the oral administration of insulin included insulin, a bile acid or alkali metal salt thereof, the bile acid being selected from the group consisting of cholic acid, chenodeoxycholic acid, taurocholic acid, taurochenodeoxycholic acid, glycocholic acid, glycochenocholic acid, 3.beta-hydroxy-12-ketocholic acid, 12. alpha-3.beta-dihydrocholic acid, and ursodesoxycholic acid, and a protease inhibitor. The composition was provided withan enterocoating to assure passage through the stomach and release in the intestine.

Kitao*et al*. [4] proposes pharmaceuticalcompositions for rectal administration of insulin. ThePharmaceutical compositions include insulin and fatty acidshaving 8 to 14 carbon atoms and nontoxic salts.

1.1 NOVEL DRUG DELIVERY SYSTEMS FOR INSULIN

Various noninvasive routes for delivery of insulin have been investigated, the most significant being oral, ocular, rectal, pulmonary, buccal, transdermal and vaginal.

1.1.1 OCULAR DELIVERY

Eye, as a portal for drug delivery is generally used for the local therapy as against systemic therapy in order to avoid risk of eye damage from high blood concentration of drugs, which are not intended for eye [5].

Pillion et al studied systemic absorption of insulin via eyedrops. It was observed that insulin in the concentration of 2 mg/ml in saline alone was not absorbed significantly. But addition of various emulsant agents increased the systemic insulin levels and concomitantly, blood glucose levels were decreased [6]. Not all emuslant agents accelerated the absorption of insulin from eyedrops. Brij-78, BL-9, saponin and several alkylglycosides were found to increase the absorption of insulin.

A reverse micelle system bearing insulin was developed for controlled and prolonged release of drug through ocular route by Jain et al [7]. Cetyl tri-ammonium bromide and span-60 were used separately with organic solvent isopropyl myrisate to prepare the reverse micelle system. It was conclude that the prolonged and controlled delivery of insulin could be possible by using reverse micellar system because corneal surface showed charge affinity and lipoidal nature, thus facilitates the drug transport across the ocular membrane and also reduces the drug drainage with the tears.

Chiou [8] proposed compositions for systemic delivery ofinsulin through the eyes where the drug passes into thenasolacrimal duct and becomes absorbed into circulation.The composition included insulin and an enhancing agent. The enhancing agents proposed include, either alone or incombination, surfactants such

as polyoxyethylene ethers offatty acids and bile salts and acids such as cholic acid,deoxycholic acid, glycocholic acid, glycodeoxycholic acid,taurocholic acid, taurodeoxycholic acid, sodium cholate,sodium glycocholate, glycocholate, sodium deoxycholate, sodium taurodeoxycholate, chenodeoxycholic acid, and ursodeoxycholicacid. The enhancer was present in a concentrationranging from 0.1% to 5% (w/v).

Yung-Chi et al [9] utilized both in vitro flow-through and in vivo device removal methods to determine the dissolution rate of insulin from gelfoam based eye device. The in vitro results indicates that the release of insulin from the device is flow-rat dependent. The in vivo data suggested that there is a direct relationship between blood glucose lowering and the rate of release of insulin from the device. Yung-Chi et al [10] prepared several ocular devices such as gelfoam(absorbable gelatin sponge) , surfactant free devices containing either sodium or zinc insulin prepared with diluted acetic or hydrochloric acid. All devices were 6.0 mm in diameter .devices were punched from a 2.0 mm thick gelfoam sponge with the aid of a common hole punch. All the insulin loaded devices were well tolerated by rabbits. The systemic absorption of insulin from the device was be enhanced by using a 5% or higher concentration of acetic acid solution as well as 1% HCl solution. In another study

Yung-Chi et al [11] developed an ocular insert for the controlled systemic delivery of insulin. Brij-78 was found to give a substantial improvement in insulin activity and a significant prolongation in its duration compared with eyedrops.

1.1.2 NASAL DELIVERY

Nasal administration may be promising route for long term systemic delivery particularly when the drug is ineffective orally due to first-pass metabolism [12, 13].

Small lipophilic molecules are generally well absorbed through the nasal mucosa. Mitraet al [14] explored lipid emulsion based formulations of insulin as an enhancer of nasal absorption. The nasal absorption of insulin in o/w vehicles was significantly enhanced in higher dose of insulin (above 5 U/ml) in both in situ and in vivo animal models.Nolte, *et al*. [15], and Bruice*et al*. [16], reported insulin preparations for nasal administration containing sodium glycolate or sodium taurofusidate as an absorption promoter. However, these absorption promoters have problems in irritation on the nasal mucosa, and the preparations have not been put in practice yet.On the other hand, a powdery composition for nasaladministration excellent in absorption through the nasalmucosa comprising a polypeptide and a water-absorbing andwater-insoluble base material was prepared [17]. It isclaimed that the nasal absorption of the polypeptide withoutusing an absorption promoter had been achieved in thecomposition.

1.1.3 PULMONARY DELIVERY

Pulmonary delivery is also important and is effected in a variety of ways - via aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers, DPIs) and solutions (nebulizers), all of which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers.

Backstrom*et al*. [18] proposed a therapeutic preparationfor inhalation that includes insulin and a substance, whichenhances the absorption of insulin in the lower respiratorytract. The enhancer is preferably a sodium salt of a saturatedfatty acid of carbon chain length 10 (i.e., sodium caprate), 12(sodium laurate), or 14 (sodium myristate). Potassium andlysine salts of capric acid are also proposed. Backstrom*et al*.noted that if the carbon chain length is shorter than about 10,the surface activity of the surfactant may be too low, and ifthe chain length is longer than about 14, decreased solubilityof the fatty acid in water limits its usefulness.

1.1.4 TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery avoids problems such as gastrointestinal irritation, metabolism, variations in delivery rates and interference due to the presence of food. It is also suitable for unconscious patients. Various methods have been developed for enhancing the transdermal delivery of insulin including improvedpassive diffusion carriers for increasing the permeability ofthe epidermis, sonophoresis, iontophoresis and ionosonictransport.Jang *et al*. [19] disclosed a patch containing insulin formulated in a gel for the iontophoretically driven transdermal delivery of insulin.

1.1.5 ORAL DELIVERY

Oral route is the most attractive and convenient route of administration. Digestive enzymes in the GI tract rapidly degradeinsulin, resulting in biologically inactive breakdownproducts. In the stomach, orally administeredinsulin undergoes enzymatic proteolysis and acidicdegradation. Various strategies have been used in attempts to improve oral and parenteral delivery ofpolypeptides. Attempts have been made to use emulsions as matrices for drug delivery of labile drugs (e.g., drugs such asinsulin, which are susceptible to enzymatic, chemical, or physical degradation). However, in spite of preliminary reports on the efficacy of emulsion formulations in promoting the intestinal absorption of insulin in rats and rabbits [20], subsequent research was abandoned because of the lability of the insulin and the need for excessive doses to maintain glucose homeostasis [21,22].

1.2 POLYMERIC SYSTEMS OF DELIVERY

Desirable patterns of drug administration have been achieved by sustained dug release from several polymers.

Torrado*et al* [23] studied the effects of viscosity and hydrophilic characteristics of different PLGA polymers on the microencapsulation of insulin in vitro and in vivo after subcutaneous administration to hyperglycemic rats. Hydrophilic PLGA polymers produced a higher burst effect than the hydrophobic ones. Moreover, an incomplete insulin release was observed with the hydrophilic PLGA polymers in comparison with the hydrophobic ones.

Su *et al* [24] formulated a polymeric delivery system based on microparticles. The amount of insulin was quantified by the improved Bradford method. It was shown that water-soluble chitosan/insulin/tripolyphosphate(TPP) mass ratio played an important role in microparticles formation. Stable, uniform, and spherical water-soluble chitosan microparticles (WSC-MPs) with high insulin association efficiency were formed at or close to optimized WSC/insulin/TPP mass ratio.

Jadon*et al* [25]developed nonionic surfactant vesicles (niosomes) to improve poor and variable oral bioavailability of griseofulvin. Niosomes were prepared by using differentnonionic surfactants span 20, span 40, and span 60. The lipid mixture consisted of surfactant, cholesterol, and dicetyl phosphate in the molar ratio of 125:25:1.5, 100:50:1.5, and 75:75:1.5, respectively. The niosomal formulations were prepared by thin film method and ether injection method. The influence of different formulation variables such as surfactant type, surfactant concentration, and cholesterol concentration was optimized for size distribution and entrapment efficiency for both methods.

Adelbary*et al* [26] prepared niosomal formulations using various surfactants (Tween 60, Tween 80 or Brij 35), in the presence of cholesterol and a negative charge inducer dicetyl phosphate (DCP) in different molar ratios and by employing a thin film hydration technique. The ability of these vesicles to entrap the studied drug was evaluated by determining the entrapment efficiency % EE after centrifugation and separation of the formed vesicles.

Saraf*et al* [27] studied the influence of formulation parameters in the preparation of sustained release enzymeloadedEudragit S100 microspheres by emulsion solvent diffusion

technique. A 3^2 full factorial experiment was designed to study the effects of the amount of solvent (dichloromethane) and stabilizers (Tween 20, 40, or 80) on the drug content and microsphere size. The results of analysis of variance test for both effects indicated that the test is significant. The effect of amount of stabilizer was found to be higher on both responses (SSY1 = 45.60; SSY2 = 737.93), whereas solvent concentration comparatively produced significant effect on the size of microspheres (SSY1 = 0.81; SSY2 = 358.83).

Pardakhty*et al* [28] prepared niosomes of polyoxyethylene alkyl ethers (Brij) for encapsulation of insulin by film hydration method. Without cholesterol, brij 35 and brij 58 did not form niosomes, apparently because of relatively large polar head groups in comparison with their alkyl chains. The size of vesicles depended on the cholesterol content, charge incorporation or hydrophilicity of surfactants. Entrapment of insulin in bilayer structure of niosomes protected it against proteolytic activity of α-chymotrypsin, trypsin and pepsin in vitro. The maximum protection activity was seen in brij 92/cholesterol (7:3 molar ratios) in which only 26.3±3.98% of entrapped insulin was released during 24 h in simulated intestinal fluid (SIF).

Schmidt *et al* [29] developed a novel controlled release formulation with PEGylated human insulin encapsulated in PLGA microspheres that produces multi-day release in vivo. The insulin is specifically PEGylated at the amino terminus of the B chain with a relatively low molecular weight PEG (5000 Da). Insulin with this modification retains full biological activity, but has a limited serum half-life, making encapsulation necessary for sustained release beyond a few hours. PEGylated insulin can be codissolved with PLGA in methylene chloride and microspheres made by a single o/w emulsion process. Insulin conformation and biological activity are preserved after PEGylation and PLGA encapsulation. The monolithic microspheres have inherently low burst release, an important safety feature for an extended release injectable insulin product.

Majumdar*et al* [30] prepared microspheres using w/o/w emulsion solvent evaporation technique with polysorbate 20 as a dispersing agent in the internal aqueous phase and PVA as a stabilizer in the external aqueous phase. PVA stabilized microspheres having maximum drug encapsulation released 2.5% insulin at pH 1.0 in 2 hours.

Ning*et al*[31] prepared and investigated the potential of the niosomes vaginal delivery system for systemic treatment of insulin. Two kinds of vesicles with Span 40 and Span 60 were prepared by lipid phase evaporation methods with sonication. The niosomal entrapment efficiency was determined by column chromatography. The particle size and morphology of the vesicles also were evaluated. The results showed optimized niosomes prepared in this study had niosomal

entrapment efficiency 26.68±1.41% for Span 40 and 28.82±1.35% for Span 60, respectively. The particle sizes of Span 40 niosomes and Span 60 niosomes were 242.5±20.5nm and 259.7±33.8 nm, respectively. There were no significant differences in appearance between the two types of vesicles.

Kofuji*et al*[32] prepared Chitosan (CS) gel beads in a 10% (w/v) aqueous amino acid solution (pH 9.0) as a vehicle for delivering peptide and protein drugs. CS gel beads with a weight-average molecular weight of (16–280) £104 were employed in this study. Preparation of the CS gel beads was affected by properties such as molecular weight and degree of deacetylation. Insulin, which is commonly used to assess protein drug delivery, was retained in the CS gel beads. Drug release from the CS gel beads was governed by diffusion of drug from the gel matrix. Sustained release of insulin from the CS gel beads was observed, despite the fact that insulin is a comparatively water-soluble drug, because insulin formed a complex with CS.

Paul *et al* [33] investigated the possibility of using hydroxyapatite ceramic microspheres loaded with insulin as an implantable delivery system in rats. With this limited test it was shown that the loaded insulin was active and able to suppress the blood glucose level in normal rats.

1. FUTURE OPPORTUNITIES AND CHALLENGES

The key to the success of protein as pharmaceuticals is to have in place an efficient drug delivery system that allows the protein drug to gain access to their target sites at the right time and for the proper duration. Four factors that must be considered to fulfill this goal are route of administration, pattern of drug release, method of delivery, and fabrication of formulation.

Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research

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